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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,107	01/06/2004	Anton Bittner	ORT1563NP	2785

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EXAMINER
ZHOU, SHUBO

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

	Application No.	Applicant(s)
Office Action Summary	10/753,107	BITTNER ET AL.
	Examiner	Art Unit	
	Shubo (Joe) Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

    4a) Of the above claim(s) *1-6 and 8-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All b)☐ Some * c)☐ None of:

      1.☐ Certified copies of the priority documents have been received.

      2.☐ Certified copies of the priority documents have been received in Application No. _____.

      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/1/04*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____ .

DETAILED ACTION

Election/Amendments

1.   Applicants' election, with traverse, of Group III (claim 7) in the response filed 3/13/06 is

acknowledged. The traversal is on the ground that while the inventions of groups I-V are distinct,

examining all of them would not impose a serious search burden to the Office as evidenced by

the examiner's common classification of the claims for the groups. No further specific argument

is provided. This is not found persuasive because although the claims of the groups belong to a

common class, as pointed out by applicants, the inventions of the groups are distinct as they

comprise distinct steps, produce distinct results, and they are mutually exclusive and not obvious

variants. As such, examining all the inventions would involve distinct search strategies and the

search would not be coextensive. Therefore, examining all the groups would impose serious

search burden to the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-36 are currently pending, claim 7 is under examination and claims 1-6 and 8-36

are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a

nonelected invention, there being no allowable generic or linking claim. Applicant timely

traversed the restriction requirement in the reply filed on 3/13/06.

Priority

2.   It is noted that this application appears to claim subject matter disclosed in prior

Application No. 60/438,002, filed 1/6/03. A reference to the prior application must be inserted

as the first sentence(s) of the specification of this application or in an application data sheet (37

CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C.

119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121,

or 365(c), the reference must include the relationship (i.e., continuation, divisional, or

continuation-in-part) of all nonprovisional applications. If the application is a utility or plant

application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to

the prior application must be submitted during the pendency of the application and within the

later of four months from the actual filing date of the application or sixteen months from the

filing date of the prior application. If the application is a utility or plant application which

entered the national stage from an international application filed on or after November 29, 2000,

after compliance with 35 U.S.C. 371, the specific reference must be submitted during the

pendency of the application and within the later of four months from the date on which the

national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date

of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not

extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where

applicable, within this time period is considered a waiver of any benefit of such prior

application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the

required time period may be accepted if it is accompanied by a grantable petition to accept an

unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition

must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR

1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under

37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due

under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The

Director may require additional information where there is a question whether the delay was

unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for

Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period

set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application

data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath

or declaration or the application transmittal letter), and the information concerning the benefit

claim was recognized by the Office as shown by its inclusion on the first filing receipt, the

petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required.

Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an

amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Information Disclosure Statement

3.   The Information Disclosure Statement filed 9/1/04 has been entered and references

therein have been considered. Initialed copies of the form PTO-1449 are enclosed herein.

Specification

4.   The specification is objected to because of the following:

Trademarks are used in this application, such as GENBANK on page 16 and

DYNABEADS on page 23. Trademarks should be capitalized wherever they appear and be

accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary

nature of the marks should be respected and every effort made to prevent their use in any manner

which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections-35 USC § 101

5.   35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of
> matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions
> and requirements of this title.

6.   Claim 7 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-

statutory subject matter.

The claim is drawn to a process for quality control of microarray analysis of gene

expression. The process comprises retrieving intensity data from replicate spots on a hybridized

microarray, calculating a mean and a standard deviation for the data, generating a Z-score

transformation for each spot, calculating a first percentage of spots for which the absolute value

of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second

percentage for which the absolute value of the z-score exceeds 2, comparing this percentage with

a predefined value, calculating a third percentage for which the absolute value of the z-score

exceeds 3, and comparing this third percentage with a predefined value.

Consideration of the "Computer-Related Inventions", section 2106 of the MPEP, part IV,

and the "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter

Eligibility" (OG Notices: 22 November 2005, available from the PTO website at

http://www.uspto.gov/web/offices/com/sol/og/2005/week47/og200547.htm, a copy of which is

enclosed herein) revealed that the instant claim is directed to non-statutory subject matter. The

claimed invention is a process of manipulating and converting data that neither results in any

physical transformation outside of the computation, nor produces a useful, concrete and tangible

result. The method steps of the claim merely retrieve gene expression data, calculating means,

deviations, z-scores and percentages, and comparing the percentages with predefined values.

The end result of the method steps is a comparison between certain percentages and predefined

values, which is not a useful, concrete and tangible result.

Claim Rejections - 35 USC § 103

7.   The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in
> section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are
> such that the subject matter as a whole would have been obvious at the time the invention was made to a person
> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the
> manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459

(1966), that are applied for establishing a background for determining obviousness under 35

U.S.C. 103(a) are summarized as follows:

1.   Determining the scope and contents of the prior art.
2.   Ascertaining the differences between the prior art and the claims at issue.
3.   Resolving the level of ordinary skill in the pertinent art.
4.   Considering objective evidence present in the application indicating obviousness
        or nonobviousness.

This application currently names joint inventors. In considering patentability of the

claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c)

and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8.   Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al.

(Genome Biology, 2002, 3(11): research0062.1-0062.12) in view of Churchill, G.A. (Nature

Genetics Supplement, Vol. 32, December 2002, pages 490-495).

The claim is drawn to a process for quality control of microarray analysis of gene

expression comprising retrieving intensity data from replicate spots, calculating a mean for the

intensity data for the spots, calculating a standard deviation for the data, generating a Z-score

transformation for each spot, calculating a first percentage of spots for which the absolute value

of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second

percentage for which the absolute value of the z-score exceeds 2, comparing this percentage with

a predefined value, calculating a third percentage for which the absolute value of the z-score

exceeds 3, and comparing this third percentage with a predefined value. Absent an explicit

definition in the specification, the term "replicate spots" is interpreted as including duplicate

spots on the same array.

Yang et al. disclose a method for assessing variability and increasing reproducibility of

microarray analysis by using replicates. They devised a simple procedure for identifying and

eliminating low-quality data for replicas within and between microarray slides. See page 0062.1,

Abstract. The method comprises using self-self hybridization, i.e. aliquots of the same RNA

being labeled separately with Cy3 or Cy5 dyes and co-hybridized to the same cDNA microarray

that contains 19,200 elements (9,600 elements in duplicate). See page 0062.2, right column.

Since all these spots comprise duplicates of each element, they are interpreted as being replica

spots. Among other things, Yang et al. tested the self-self hybridization using RNA sample from

a cell line KM12L4A. In the method, intensity data for each spot is obtained and normalized, and

a standard z-score is calculated based on intensity. Specifically, using a sliding window of fixed

width in log10(Cy5*Cy3), the local mean and SD was calculate for each gene using the

normalized data. Figure 3a on page 0062.5 depicts the results of such a calculation for cell line

KM12L4A, with data less than 1SD shown blue, between 1SD and 2SD in green, and greater

than 2SD in red, respectively. Note that the copy of the reference provided to applicants as

enclosed herein is a black and white copy of the original color picture, which is available from

Genome Biology online at http://genomebiology.com/content/pdf/gb-2002-3-11-

research0062.pdf. For the convenience of the present discussion, based on the original Figure 3a,

the portions of the figure represented by colors of blue, green and red are indicated with B, G and

R, respectively, by the examiner in the copy enclosed herein.

It is pointed out that while Yang et al. do not explicitly state that the z-score is calculated

by subtracting the mean from the intensity data of a replica spot and dividing by the standard

deviation for the intensity data, as recited in claim 7, it would be readily apparent to one of

ordinary skill in the art that this is how z-score is calculated in the art of statistical analysis. See

enclosed definition and formula for calculating standard score, also called z-score or normal

score, printed from Wikipedia online at < http://en.wikipedia.org/wiki/Z-score> on 5/18/06.

Thus, Yang et al. implicitly disclosed that the z-score is calculated by subtracting the mean from

the intensity data of a replica spot and dividing by the standard deviation for the intensity data.

Yang et al. do not explicitly disclose calculating a first percentage of spots for which the absolute value of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second percentage for which the absolute value of the z-score exceeds 2, comparing this percentage with a predefined value, calculating a third percentage for which the absolute value of the z-score exceeds 3, and comparing this third percentage with a predefined value.

Churchill teaches fundamentals of experimental design for cDNA microarrays. Churchill analyzes the importance of duplications/replications in designing array experiments, as depicted in Figure 1 on page 491, including treatment replication, biological replication, dye and technical replication, spot and array duplications. Churchill states that "the correlation observed between ratios of fluorescent intensity from duplicate spots on a single microarray slide will typically exceed 95% ... However, if the same target sample is divided and hybridized to two different microarray slides, the correlation across hybridizations is likely to fall to the 60 to 80% range, somewhat lower if the dye labeling is reversed. Correlation between samples obtained form individuals inbred mice may be as low as 30%. If the experiments are carried out in different laboratories, the correlations may be lower still." See page 490, right column.

Yang et al. state that in analysis of differential gene expression, only genes with a greater than 2 SD from the mean (i.e. $z > 2$) are identified as being significantly differentially expressed. Since Figure 3a represents data from self-self hybridization, it would have been obvious to one of ordinary skill in the art that the elements with a z-score of higher than 2 SD would represent elements with unacceptable variations, and the percentage of the number of such elements on an microarray would indicate the overall quality of the array: the lower the percentage, the higher the quality. Similarly, the percentage of the number of elements with a z-score less than 2 SD,

e.g. more or less than 1, would also indicate the quality of the array: the higher the percentage, the higher the quality of the array. Furthermore, Yang et al. analyzed data variability and reproducibility using triplicates and showed that the spots of outliers in the arrays tested are generally around 5%. See page 0062.5. Yang et al. stressed that replication is essential for ensuring data quality.

One of ordinary skill in the art would have been motivated by Churchill to design microarray experiments using different layers of replications and/or duplications to minimize variations and increase correlations, and motivated by Yang et al. to use self-self hybridizations to evaluate variations and thus quality of the array. Given that the variations in these different replications and/or duplications are different as shown by the different percentage of correlations taught by Churchill, and that the quality of an array would be indicated by the percentage of the number of spots with the absolute values of z-scores of 1, 2 or 3 (i.e. >2) as implied by Yang et al. in Fig. 3a, one of ordinary skill in the art would have been motivated by Yang et al. to determine the percentages of the absolute values of z-scores of 1, 2, and 3, respectively, in these different experimental designs with different replications and/or duplications in order to better and more precisely evaluate the quality of an array. It would have been obvious that the higher the percentage of spots with an absolute value of z-score of 1 or less, and or 2 or less, the higher the quality of the array; conversely, the higher the percentage of spots with an absolute value of z-score of 2 or more, and/or 3 or more, the lower the quality of the array. Thus, in a microarray quality control experiment using z-scores, calculating a first percentage of spots for which the absolute value of the z-score exceeds 1, comparing the percentage with a predefined value, calculating a second percentage for which the absolute value of the z-score exceeds 2, comparing

this percentage with a predefined value, calculating a third percentage for which the absolute

value of the z-score exceeds 3, and comparing this third percentage with a predefined value

would have been obvious to a person having ordinary skill in the art at the time the invention was

made.

Conclusion

9.   No claim is allowed.

10.   Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724.

The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can

be reached on 571-272-0811.The fax phone number for the organization where this application

or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the

status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose

phone number is (571) 272-0549.

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USPTO Call Center (UCC) at 800-786-9199.

Shubo (Joe) Zhou, Ph.D.

Patent Examiner